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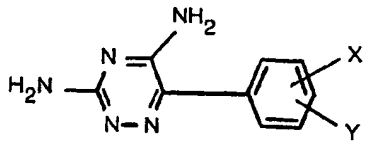
1,2,4-Triazine derivatives, process for preparing such compounds and pharmaceutical compositions containing them

The present invention relates to a group of novel compounds which are useful in the treatment of CNS disorders, such as epilepsy, to pharmaceutical compositions containing them, and to methods for their preparation.

U.K. Patent No. 759,014 discloses compounds of the formula (I):

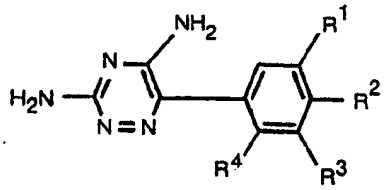


(I)

wherein X and Y are hydrogen and/or halogen atoms, as having activity against bacterial and malerial infections in animals. This patent specifically discloses those compounds wherein X and Y are both hydrogen atoms, wherein X is a hydrogen atom and Y is a 4-chloro atom, and wherein X is a 4-chloro atom and Y is a 2-chloro and 3-chloro atom, respectively.

Rees *et al, J. Med. Chem.* 1972 *15,* 859, have shown that these compounds, and in particular the 4-chlorophenyl and the 3,4-dichlorophenyl compounds are active against the malaria organism *Plasmodium berghei* in mice. However, these two compounds were also shown to be toxic at curative doses and presumably were not investigated further because of their low therapeutic ratio in this context. The 2,4-dichlorophenyl compound had only slight antimalarial activity. The therapeutic ratio of the compounds were such as to prevent their use in human medicine for the treatment or prophylaxis of malaria and they were not progressed further.

US Patent No. 3,637,688 discloses compounds of the formula (II):



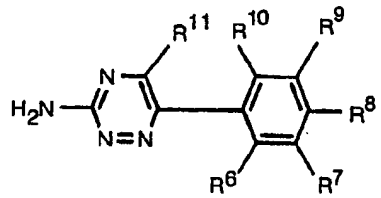
(II)

wherein R^1 is hydrogen or fluorine, and R^2, R^3 and R^4 are hydrogen, fluorine or trifluoromethyl provided that at least one of R^1, R^2, R^3 and R^4 is fluorine or trifluoromethyl, as being useful in the treatment of malaria. In the Rees article referred to above, the 4-trifluoromethylphenyl compound (II; $R^2 = CF_3$, $R^1 = R^3 = R^4 = H$) was claimed to be less toxic than the chlorophenyl compounds whilst still being active against malaria. The other fluoro and trifluoromethyl compounds referred to in the article were substantially less active than the 4-trifluoromethylphenyl compound.

Rosenburg and Bottiroli *Proc. Soc. exp. Biol.,* 1964, *115,* 410, described a series of tests in which three anti-malarial agents, quinacrine, chloroquine and hydroxychloroquine, were tested as anti-convulsants. Only hydroxychloroquine possessed a favourable activity profile.

It has now been discovered that a group of novel 3,5-diamino-6-(substituted phenyl)-1,2,4-triazines are active in the treatment of CNS disorders, such as psychiatric and neurological disorders, and are particularly useful as anticonvulsants, for example in the treatment of epilepsy. Furthermore, these triazines are believed to be nondepressant at likely therapeutic dose levels and therefore are advantageous as compared with depressant antiepileptics such as phenobarbitone.

Accordingly the present invention provides a compound of the formula (III):



(III)

or an acid addition salt thereof,

wherein R^6 is chlorine, bromine, iodine, C_{1-4} alkyl or trifluoromethyl; R^7 is hydrogen, halogen C_{1-4} alkyl or trifluoromethyl or R^6 and R^7 form a —CH=CH—CH=CH— group optionally substituted by a halogen atom or a C_{1-4} alkyl or trifluoromethyl group,

R^8 is hydrogen, bromine, iodine, C_{1-4} alkyl or trifluoromethyl, R^9 is hydrogen, halogen, C_{1-4} alkyl or trifluoromethyl, R^{10} is hydrogen, methyl, or fluorine and R^{11} is an amino, C_{1-4} acylamino or di-substituted aminomethyleneamino group provided that, at most, only two of R^7—R^{10} are other than hydrogen and that R^7—R^{10} are not all hydrogen when R^8 is chlorine.

Suitably the C_{1-4} alkyl group is a methyl group.

Suitably R^8 is a chlorine or bromine atom or a methyl or trifluoromethyl group or is linked to R^7 to form a —CH=CH—CH=CH— group and preferably R^8 is a chlorine or bromine atom or linked to R^7 to form a —CH=CH—CH=CH— group.

Preferably R^7 and R^9 are each hydrogen, chlorine or bromine atoms.

Preferably R^8 is a hydrogen or bromine atom.

Suitable substituents for the aminomethylene amino group are C_{1-4} alkyl groups or a $-(CH_2)_2X(CH_2)_n-$ group wherein X is O, S, NH or CH_2 group and n is the integer 1 or 2.

Suitably R^{11} is an amino, acetamido or dimethylaminomethyleneamino group and preferably R^{11} is an amino group.

When three of the substituents R^8—R^{10} are other than hydrogen, it is preferred that R^9 and R^{10} are hydrogen and that R^8, R^7 and R^9 are those halogen atoms previously defined and in particular chlorine atoms.

Preferred compounds of the formula (III) include:
3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine
3,5-diamino-6-(2,5-dichlorophenyl)-1,2,4-triazine
3,5-diamino-6-(4-bromo-2-chlorophenyl)-1,2,4-triazine
3,5-diamino-6-(5-bromo-2-chlorophenyl)-1,2,4-triazine
3,5-diamino-6-(2,3,5-trichlorophenyl)-1,2,4-triazine
3,5-diamino-6-(2-chloro-6-fluorophenyl)-1,2,4-triazine
3,5-diamino-6-(2-methylphenyl)-1,2,4-triazine
3,5-diamino-6-(2-trifluoromethylphenyl)-1,2,4-triazine
3,5-diamino-6-(2-bromophenyl)-1,2,4-triazine
3,5-diamino-6-(2-iodophenyl)-1,2,4-triazine
3,5-diamino-6-(2-bromo-5-chlorophenyl)-1,2,4-triazine
3,5-diamino-6-(1-naphthyl)-1,2,4-triazine
5-acetamido-3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine
3-amino-6-(2,3-dichlorophenyl)-5-dimethylaminomethyleneamino-1,2,4-triazine
3,5-diamino-6-(2-methyl-1-naphthyl)-1,2,4-triazine
3,5-diamino-6-(3-chloro-1-naphthyl)-1,2,4-triazine.

The present invention also provides the first practicable medical use of the compounds of the formula (III), as hereinbefore defined. Preferably this will be for the treatment of CNS disorders, and in particular epilepsy, in humans.

In a further aspect, the present invention provides pharmaceutical formulations comprising a compound of the formula (III) in admixture with a pharmaceutically acceptable carrier. Suitable acid addition salts of the compounds of formula (III) include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable. Thus, preferred salts include those formed from hydrochloric, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, succinic, oxalic, fumaric, maleic, oxaloacetic, methanesulphonic, *p*-toluenesulphonic and benzenesulphonic acids.

The compounds of the formula (III) will be present in the compositions of the present invention in an effective unit dosage form, that is to say in an amount sufficient to be effective against CNS disorders *in vivo*.

The pharmaceutically acceptable carriers present in the compositions of this invention are materials recommended for the purpose of administering the medicament. These may be liquid or solid materials, which are otherwise inert or medically acceptable and are compatible with the active ingredients.

These pharmaceutical compositions may be given orally or parenterally, used as a suppository, or applied topically as an ointment, cream or powder. However, oral and parenteral administration of the compositions are preferred.

For oral administration, fine powders or granules will contain diluting, dispensing and/or surface active agents, and may be presented in a draught, in water or in a syrup, in capsules or sachets in the dry state or in non-aqueous suspension wherein suspending agents may be included, or in a suspension in water or syrup. Where desirable or necessary, flavouring, preserving, suspending, thickening or emulsifying agents can be included.

When a suspension is prepared in water according to the present invention at least one such agents will be present.

For parenteral administration, the compounds may be presented in sterile aqueous injection solutions which may contain anti-oxidants or buffers.

As stated above, the free base or a salt thereof may be administered in its pure form unassociated with other additives in which case a capsule or sachet is the preferred carrier.

Alternatively the active compound may be presented in a pure form as an effective unit dosage, for instance, compressed as a tablet or the like.

Other compounds which may be included are, for example, medically inert ingredients, e.g. solid and liquid diluents such as lactose, starch, or calcium phosphate for tablet or capsules; olive oil or ethyl oleate for soft capsules; and water or vegetable oil for suspensions or emulsions; lubricating agents such as talc or magnesium stearate; gelling agents such as colloidal clays; thickening agents such as gum tragacanth or sodium alginate; and other therapeutically acceptable accessary ingredients such as humectants, preservatives, buffers, and antioxidants which are useful as carriers in such formulations.

Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the formula (III) which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 250 mg.

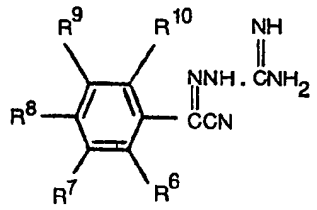
The pharmaceutical compositions of the present invention will be prepared by the admixture of a compound of the formula (III) with a pharmaceutically acceptable carrier. Conventional pharmaceutical excipients may be admixed as required.

The present invention provides a method of treatment of convulsions in mammals, and particularly epilepsy in humans by the administration of a non-toxic anticonvulsant effective amount of a compound of the formula (III) or a pharmaceutically acceptable salt, or a composition as hereinbefore defined.

As indicated above, the compounds of the formula (III) are generally useful in treating such disorders by oral administration or injection (*i.p.* or *s.c.*).

The compounds of the formula (III) are normally administered orally at a dose of from 0.1 mg/kg. to 30 mg/kg. per day. The dose range for adult humans is generally from 8 mg. to 2,400 mg/day and preferably 35 to 1,050 mg/day. Due to the fact that the compounds of the formula (III) are extremely long acting, it may often be advantageous to administer an initial dose of 70 to 2,400 mg. the first day then a lower dose of 20 to 1,200 mg. on subsequent days.

The present invention also provides a process for the preparation of compounds of the formula (III) which comprises the cyclisation of a compound of the formula (IV):



(IV)

wherein R^6—R^{10} are as hereinbefore defined; and thereafter, where desired substituting the amino group adjacent to the phenyl ring to give a group R^{11} wherein R^{11} is as hereinbefore defined other than amino, by conventional methods.

This cyclisation reaction is normally carried out by refluxing in an alkanol, preferably a C_{1-4} alkanol such as methanol or ethanol, in the presence of a strong base such as potassium hydroxide.

The preparation of the compounds of the formula (IV) is analogous to that described in the literature, i.e. U.S. Patent No. 3,637,688, for structurally related compounds.

The following examples illustrate the preparation of the compounds of the invention and their CNS activity.

Example 1

Preparation of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine.

2,3-Dichlorobenzoic Acid

A solution of 2,3-dichloroiodobenzene (37.3 g, 0.14M) in sodium dried ether (300 mls) was added dropwise to magnesium turnings (3.65 g, 0.15 gm Atm) and a crystal of iodine with warming so as to form a Grignard reagent.

The mixture was stirred and refluxed for 2 hours then cooled and transferred dropwise, under nitrogen; into a stirred mixture of sodium dried ether (250 mls) containing solid carbon dioxide (*ca.* 100 g). The mixture was stirred for 2 hours, left overnight to warm to room temperature, then treated with ice (*ca.* 150 g) and 2N aqueous hydrochloric acid (75 mls), and the product extracted with ether (200, 100 and 50 mls). The combined ether extracts were washed with water (2 x 40 mls) then repeatedly extracted with 2N aqueous sodium hydroxide (100, 50 and 50 mls). These basic solutions were combined, stirred with activated charcoal (3 g) for 10 minutes, filtered and the cooled filtrate was acidified with concentrated hydrochloric acid (25 mls) at 10°C. The resultant solid was filtered off, washed with water (2 x 20 mls) and dried *in vacuo*. Yield 20.76 g (77.6%), m.p. 167—169°C (uncorrected).

2,3-Dichlorobenzoyl Chloride

A mixture of 2,3-dichlorobenzoic acid (39.4 g 0.2M) and thionyl chloride (100 mls) was heated to reflux for 2½ hours. The cooled solution was evaporated down *in vacuo* and distilled under nitrogen. Yield 35.5 g (85%), b.p. 146—148°C at 31 mm of mercury pressure.

2,3-Dichlorobenzoyl Cyanide

A mixture of cuprous cyanide (36.9 g, 0.41M), potassium iodide (68.5 g, 0.41M) and xylene (400 mls) was refluxed in an atmosphere of nitrogen under a Dean and Stark trap for 24 hours so as to remove all trace of water.

A solution of 2,3-dichlorobenzoyl chloride (35.5 g, 0.17M) in sodium dried xylene (130 mls) was added dropwise to the above mixture of dry cuprous cyanide and xylene. The resulting mixture was stirred and heated to reflux for a further 72 hours. The cooled mixture was filtered and the solid washed well with sodium dried xylene (200 mls). The filtrate and washings were combined and evaporated down *in vacuo* to give an oil. Yield 32 g (94%).

3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine

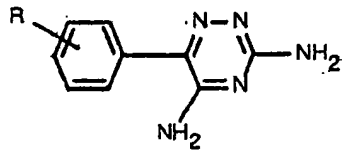
A solution of 2,3-dichlorobenzoyl cyanide (32 g, 0.16M) in dimethylsulphoxide (80 mls) was added dropwise to a stirred suspension of aminoguanidine bicarbonate (81.67 g, 0.6M) which had been treated with 8N aqueous nitric acid (400 mls) at a temperature of *ca* 25°C. The mixture was stirred for 3 hours, then left to stand at room temperature for 7 days. The cooled mixture was stirred and basified with 0.880 aqueous ammonia (400 mls) at 20°C, then stirred with ice cooling for 30 minutes, filtered and the resulting solid washed thoroughly with water and finally dried *in vacuo*.

The above solid was added to a 10% solution of potassium hydroxide pellets in methanol (400 mls) and the solution heated to refluxed for 1½ hours. When cool the solution was evaporated down *in vacuo*, treated with ice water (800 mls) then stirred for 30 minutes and filtered. The residue was dried and recrystallised from isopropanol to give 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine. Yield 6.8 g (15.6%), m.p. 216—218°C (uncorrected).

Example 2

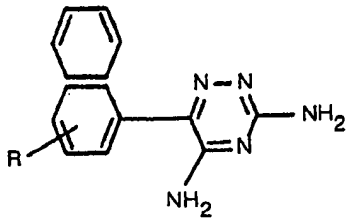
By a method analogous to that described in Example 1 the compounds listed in Tables 1 and 2 were prepared:

TABLE 1



V; R	m.p. (uncorrected)	% Yield (from acid)
2,5–Cl_2	228–230°C	2
2–Cl, 4–Br	223–225°C	6
2–Cl, 5–Br	238–240°C	2
2–CF_3	177–178°C	0.4
2–Cl, 6–F	226–228°C	14.5
2–Me	181–183°C	25
2–Br	204–207°C	34
2–I	219–222°C	7
2–Br, 5–Cl	255–256°C	1.2

TABLE 2



VI; R	m.p. (uncorrected)	% Yield (from acid)
H	215–216°C	7.5
2–Me	131–134°C	0.3
3–Cl	285–286°C	1.0

Example 3

Preparation of 3,5-diamino-6-(2,3,5-trichlorophenyl)-1,2,4-triazine

2,3,5-Trichlorobenzoic Acid

Powered sodium nitrite (37.0 g, 0.54M) was added portionwise to concentrated sulphuric acid (270 ml) which was stirred under an atmosphere of nitrogen. The temperature of the mixture was not allowed to rise above 70°. Meanwhile 3-amino-2,5-dichlorobenzoic acid (100 g, 0.45M) was dissolved in hot glacial acetic acid (1,200 ml), the resultant solution was cooled rapidly to room temperature and added dropwise to the above stirred and cooled nitrous acid mixture so that the internal temperature did not rise above 30°. The solution formed after the addition was left at room temperature for 2 hours then was slowly added to a stirred solution of cuprous chloride (97 g, 0.97M) in concentrated hydrochloric acid (970 ml). The resultant mixture was stirred until the nitrogen evolution had ceased and was then left overnight. The solid was filtered off, washed well with water and dried *in vacuo*. Yield 90.1 g (89%) m.p. 164—165°C (uncorrected).

2,3,5-Trichlorobenzoyl Chloride

A mixture of 2,3,5-trichlorobenzoic acid (90 g, 0.4M) and dimethylformamide (1 ml) in thionyl chloride (200 ml) was heated to reflux for 2 hours. The cooled solution was evaporated down *in vacuo* and the residue distilled under nitrogen. Yield 89.2 g (90%), b.p. 158—160°C at the pressure of 30 mm of mercury.

2,3,5-Trichlorobenzoyl Cyanide

A mixture of cuprous cyanide (89 g, 0.9M), potassium iodide (150.5 g, 0.9M) and xylene (800 ml) was heated to reflux in an atmosphere of nitrogen under a Dean and Stark trap for 24 hours.

A solution of 2,3,5-trichlorobenzoyl chloride (89 g, 0.36M) in sodium dried xylene (100 ml) was added to the above suspension. The resulting mixture was stirred and heated to reflux for a further 72 hours. The cooled mixture was filtered and the solid was washed well with sodium dried xylene (200 ml). The filtrate and washings were combined and evaporated *in vacuo* to give an oil. Yield 76 g (96%).

3,5-Diamino-6-(2,3,5-trichlorophenyl)-1,2,4-triazine

A solution of 2,3,5-trichlorobenzoyl cyanide (38.5 g, 0.16M) in dimethylsulphoxide (80 ml) was added dropwise to a stirred suspension of aminoguanidine bicarbonate (65.76 g, 0.32M) which had been treated with 8N aqueous nitric acid (560 ml). The mixture was stirred for 3 hours and then was left to stand at room temperature for 21 days. The solid was filtered off, washed with water (2 x 100 ml) and dried *in vacuo*. A suspension of the dried solid in a 10% solution of potassium hydroxide pellets in methanol (320 ml) was heated to reflux for 1 hour, the mixture was cooled and evaporated down *in vacuo*. The residue was treated with ice/water (200 ml), the resultant solid was filtered off and dried *in vacuo*. This dried solid was put on top of a dry column (25 mm diameter, 200 g of MFC silica gel) and eluted with a solution of ethyl acetate/methanol/acetic acid (90:2.5:2.5). Fractions 50 to 80 (900 drops per fraction) were collected, combined and evaporated down *in vacuo*. The resultant solid was recrystallised from isopropanol to give 3,5-diamino-6-(2,3,5-trichlorophenyl)-1,2,4-triazine. Yield. 0.77 g (1.6%), m.p. 232—235°C (uncorrected).

Example 4

Preparation of 5-Acetamido-3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine

A solution of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (2 gm, 8mM) and acetic anhydride (10 mls) in acetic acid (20 mls) was stirred and heated to reflux for 2 hours. The solution was then cooled and evaporated down *in vacuo*. The residue was treated with aqueous 0.880 ammonia (100 mls) and the resultant mixture was stirred for 2 hours. The solid was separated by filtration, dried then recrystallized from isopropanol to give 5-acetamido-3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine. Yield 1.0 gms (42%), m.p. 250—252° (uncorrected).

Example 5

Preparation of 3-Amino-6-(2,3-dichlorophenyl)-5-dimethyl aminomethyleneamino-1,2,4-triazine oxalate

Dimethylformamide dimethyl acetal (1 ml) was added dropwise to a stirred mixture of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (1 g, 4mM) in dry dimethylformamide (20 mls) in a nitrogen atmosphere. The mixture was stirred and heated at 120° for 2 hours, the the resultant solution was cooled and evaporated down *in vacuo*. The residual oil was washed once with water (20 mls) then dissolved in a solution of oxalic acid (1 gm) in methanol (20 mls). Ether (100 mls) precipitated an oil which slowly crystallized. The residue was recrystallized from aqueous isopropanol to give 3-amino-6-(2,3-dichlorophenyl)-5-dimethylaminomethyleneamino-1,2,4-triazine oxalate. Yield 0.19 gms (14%), m.p. 172—175°C Dec. (uncorrected).

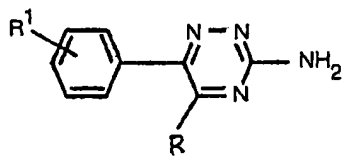
Example 6

Pharmacological Activity of Compounds of the Present Invention

Tables 3 and 4

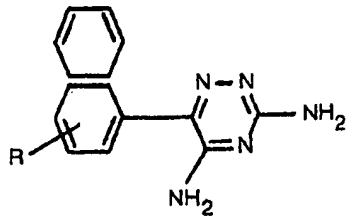
The anticonvulsant activity of certain compounds of the present invention was determined by a standard maximal electroshock test, that described by L. A. Woodbury and V. D. Davenport, *Arch. Int. Pharmacodyn.*: 1952, *92*, 97.

TABLE 3



VII; R^1	VII; R	ED_{50}, MES mice, mg/kg, p.o.
2,3–Cl_2	NH_2	2.4
2,5–Cl_2	NH_2	3.3
2–Me	NH_2	15.0
2–Cl, 4–Br	NH_2	12.8
2–Cl, 5–Br	NH_2	6.0
2–CF_3	NH_2	20.0
2–Cl, 6–F	NH_2	12.2
2,3,5–Cl_3	NH_2	0.65
2–Br	NH_2	8.5
2–I	NH_2	11.8
2–Br, 5–Cl	NH_2	4.6
2,3–Cl_2	$NHCOCH_3$	5
2,3–Cl_2	$N{=}CHNMe_2$	5

TABLE 4



VIII R	ED_{50}, MES mice, mg/kg, p.o.
H	2.9
2–Me	16.5
3–Cl	6.5

The LD_{50}'s (expressed in mg/kg, p.o.) of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine and 3,5-diamino-6-(2,5-dichlorophenyl)-1,2,4-triazine were determined in mice and rats. The LD_{50} described is the dose for which 50% of the animals survive 10 days after administration of the compound.

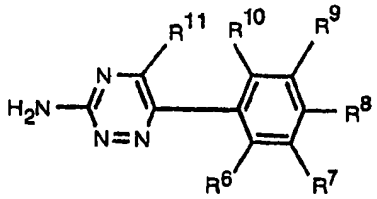
VII R^1	R	Mice	Rats
2,3–Cl_2	NH_2	250	640
2,5–Cl_2	NH_2	708	640

3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine	150 mg	contents per tablet
Lactose	200 mg	
Maize Starch	50 mg	
Polyvinylpyrrolidone	4 mg	
Magnesium Stearate	4 mg	

The drug was mixed with the lactose and starch and granulated with a solution of the polyvinylpyrrolidone in water. The resultant granules were dried, mixed with magnesium stearate and compressed to give tablets of average weight 408 mg.

Claims

1. A compound of the formula (III):



(III)

or an acid addition salt thereof, wherein R^6 is chlorine, bromine, iodine, C_{1-4} alkyl or trifluoromethyl; R^7 is hydrogen, halogen, C_{1-4} alkyl or trifluoromethyl or R^6 and R^7 form a —CH=CH—CH=CH— group optionally substituted by a halogen atom or a C_{1-4} alkyl or trifluoromethyl group; R^8 is hydrogen,

bromine, iodine, C_{1-4} alkyl or trifluoromethyl; R^9 is hydrogen, halogen, C_{1-4} alkyl or trifluoromethyl; R^{10} is hydrogen, methyl or fluorine and R^{11} is amino, C_{1-4} acylamino or di-substituted aminomethyleneamino, provided that at most only two of R^7—R^{10} are other than hydrogen and that R^7—R^{10} are not all hydrogen when R^6 is chlorine.

2. A compound of the formula (III), as claimed in claim 1 herein, wherein R^6 is a chlorine or bromine atom, R^7 is a hydrogen, chlorine or bromine atom or R^8 is linked to R^7 to form a —CH=CH—CH=CH— group, R^9 is a hydrogen, chlorine or bromine atom, R^8 is a hydrogen or bromine atom and R^{11} is an amino group.

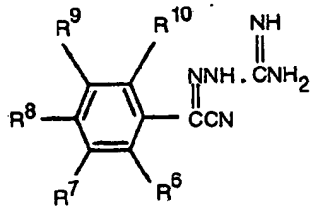
3. 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine.

4. A pharmaceutical composition comprising a compound of the formula (III), as claimed in any of claims 1 to 3 herein, in admixture with a pharmaceutically acceptable carrier.

5. A compound of the formula (III), as claimed in any one of claims 1 to 3 herein, for use in medicine.

6. A compound of the formula (III) as claimed in any one of claims 1 to 3 for use in medicine in the treatment of epilepsy.

7. A process for the preparation of a compound of the formula (III), as claimed in claim 1 herein, which comprises the cyclisation of a compound of the formula (IV):

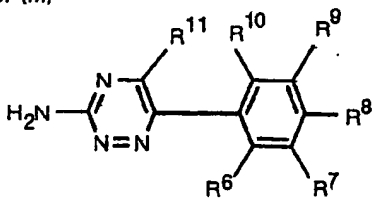


(IV)

wherein R^8—R^{10} are as defined in claim 1 herein; and thereafter, where desired, substituting the amino group adjacent to the phenyl ring to give a group R^{11} wherein R^{11} is as defined in claim 1 herein other than amino, by conventional methods.

Patentansprüche

1. Verbindung der Formel (III)



(III)

oder ein Säureadditionssalz davon, worin R^6 Chlor, Brom, Jod, C_{1-4}-Alkyl oder Trifluormethyl; R^7 Wasserstoff, Halogen, C_{1-4}-Alkyl oder Trifluormethyl oder R^8 und R^7 gemeinsam eine —CH=CH—CH=CH—Gruppe, die gegebenenfalls durch ein Halogenatom oder eine C_{1-4}-Alkyl- oder Trifluormethylgruppe substituiert ist, R^8 Wasserstoff, Brom, Jod, C_{1-4}-Alkyl oder Trifluormethyl, R^9 Wasserstoff, Halogen, C_{1-4}-Alkyl oder Trifluormethyl, R^{10} Wasserstoff, Methyl oder Fluor und R^{11} Amino, C_{1-4}-Acylamino oder disubstituiertes Aminomethylenamino, mit der Maßgabe bedeuten, daß höchstens zwei der Gruppen R^7 bis R^{10} von Wasserstoff verschieden sind und daß nicht sämtliche Gruppen R^7 bis R^{10} Wasserstoff bedeuten, wenn R^6 Chlor darstellt.

2. Verbindung der Formel (III) gemäß Anspruch 1, dadurch gekennzeichnet, daß R^6 ein Chlor- oder Bromaton darstellt, R^7 ein Wasserstoff-, Chlor- oder Bromaton bedeutet oder R^8 mit R^7 unter Bildung einer —CH=CH—CH=CH—Gruppe verbunden sind, R^9 ein Wasserstoff-, Chlor- oder Bromaton darstellt, R^8 ein Wasserstoff- oder Bromaton bedeutet und R^{11} eine Aminogruppe darstellt.

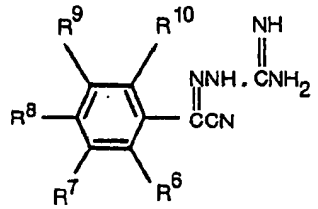
3. 3,5-Diamino-6-(2,3-dichlorphenyl)-1,2,4-triazin.

4. Pharmazeutische Zubereitung enthaltend eine Verbindung der Formel (III) gemäß einem der Ansprüche 1 bis 3 zusammen mit einem pharmazeutisch annehmbaren Träger.

5. Verbindung der Formel (III) gemäß einem der Ansprüche 1 bis 3 zur Verwendung in der Medizin.

6. Verbindung der Formel (III) gemäß einem der Ansprüche 1 bis 3 zur Verwendung in der Medizin bei der Behandlung der Epilepsie.

7. Verfahren zur Herstellung einer Verbindung der Formel (III) gemäß Anspruch 1, dadurch gekennzeichnet, daß man eine Verbindung der Formel (IV)

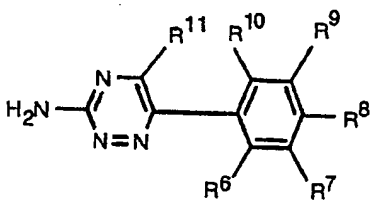


(IV)

in der R^6 bis R^{10} die in Anspruch 1 angegebenen Bedeutungen besitzen, cyclisiert und anschließend gewünschtenfalls die dem Phenylring benachbarte Aminogruppe in an sich bekannter Weise unter Bildung einer Gruppe R^{11}, die die in Anspruch 1 angegebenen Bedeutungen besitzt, jedoch von einer Aminogruppe verschieden ist, substituiert.

Revendications

1. Composé de formule (III):



(III)

ou sel d'addition d'acide de celui-ci
où R^6 représente un atome de chlore, de brome ou d'iode ou un radical alcoyle en C_{1-4} ou trifluorométhyle;
R^7 représente un atome d'hydrogène ou d'halogène ou un radical alcoyle en C_{1-4} ou trifluorométhyle ou bien
R^6 et R^7 forment un radical —CH=CH—CH=CH— éventuellement substitué par un atome d'halogène ou un radical alcoyle en C_{1-4} ou trifluorométhyle,
R^8 représente un atome d'hydrogène, de brome ou d'iode ou un radical alcoyle en C_{1-4} ou trifluorométhyle,
R^9 représente un atome d'hydrogène ou d'halogène ou un radical alcoyle en C_{1-4} ou trifluorométhyle,
R^{10} représente un atome d'hydrogène, un radical méthyle ou un atome de fluor, et
R^{11} représente un radical amino, C_{1-4} acylamino ou aminométhylèneamino disubstitué, à la condition qu'au maximum deux d'entre R^7—R^{10} représentent autre chose que des atomes d'hydrogène et que R^7—R^{10} ne représentent pas tous des atomes d'hydrogène lorsque R^6 représente un atome de chlore.

2. Composé de formule (III) suivant la revendication 1, où R^6 représente un atome de chlore ou de brome, R^7 représente un atome d'hydrogène, de chlore ou de brome ou bien R^6 est uni à R^7 pour former un radical —CH=CH—CH=CH—, R^9 représente un atome d'hydrogène, de chlore ou de brome, R^8 représente un atome d'hydrogène ou de brome et R^{11} représente un radical amino.

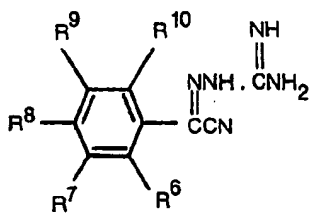
3. La 3,5-diamino-6-(2,3-dichlorophényl)-1,2,4-triazine.

4. Composition pharmaceutique comprenant un composé de la formule (III), suivant l'une quelconque des revendications 1 à 3, à l'état de mélange avec un excipient pharmaceutiquement acceptable.

5. Composé de la formule (III), suivant l'une quelconque des revendications 1 à 3, pour une application en médecine.

6. Composé de la formule (III), suivant l'une quelconque des revendications 1 à 3, pour une application en médecine dans le traitement de l'épilepsie.

7. Procédé de préparation d'un composé de la formule (III), suivant la revendication 1, qui comprend la cyclisation d'un composé de formule (IV):



(IV)

où R^8—R^{10} sont tels que définis dans la revendication 1 et ensuite, si la chose est désirée, la substitution du radical amino adjacent au radical phényle pour la formation d'un radical R^{11}, où R^{11} est tel que défini dans la revendication ci-dessus et est autre qu'un radical amino, suivant des techniques classiques.